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<b>(21) International Application Number:</b> PCT/US98/07045 <b>(22) International Filing Date:</b> 8 April 1998 (08.04.98)  <b>(30) Priority Data:</b> 08/846,254 30 April 1997 (30.04.97) US  <b>(71) Applicant:</b> EMISPHERE TECHNOLOGIES, INC. [US/US]; 15 Skyline Drive, Hawthorne, NY 10532 (US).  <b>(72) Inventors:</b> LEONE-BAY, Andrea; 20 Woodland Way, Ridgefield, CT 06877 (US). GSCHNEIDNER, David; 44 Cerritta Street #6, Stamford, CT 06907 (US). WANG, Eric; 1120 Warburton Avenue #F, Yonkers, NY 10701 (US). SARUBBI, Donald, J.; 18 Lawton Lane, Bronxville, NY 10708 (US).  <b>(74) Agents:</b> ROBINSON, Joseph, R. et al.; Darby & Darby P.C., 805 Third Avenue, New York, NY 10022-7513 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> COMPOUNDS AND COMPOSITIONS FOR DELIVERING ACTIVE AGENTS  <b>(57) Abstract</b>  Carrier compounds and compositions therewith which are useful in the delivery of active agents are provided. Methods of administration and preparation are provided as well.		

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## **COMPOUNDS AND COMPOSITIONS FOR DELIVERING ACTIVE AGENTS**

### **10 FIELD OF THE INVENTION**

The present invention relates to compounds for delivering active agents, and particularly biologically or chemically active agents. These compounds are used as carriers to facilitate the delivery of a cargo to a target. The carrier compounds are well suited to form non-covalent mixtures with  
15 biologically-active agents for oral administration to animals. Methods for the preparation administration of such compositions are also disclosed.

### **BACKGROUND OF THE INVENTION**

Conventional means for delivering active agents are often severely  
20 limited by biological, chemical, and physical barriers. Typically, these barriers are imposed by the environment through which delivery occurs, the environment of the target for delivery, or the target itself. Biologically or chemically active agents are particularly vulnerable to such barriers.

For example in the delivery to animals of biologically active or  
25 chemically active pharmacological and therapeutic agents, barriers are imposed by the body. Examples of physical barriers are the skin and various organ membranes that must be traversed before reaching a target. Chemical barriers include, but are not limited to, pH variations, lipid bi-layers, and degrading enzymes.

30 These barriers are of particular significance in the design of oral delivery systems. Oral delivery of many biologically or chemically active agents would be the route of choice for administration to animals if not for biological, chemical, and physical barriers such as varying pH in the gastro-intestinal (GI) tract, powerful digestive enzymes, and active agent impermeable gastro-

intestinal membranes. Among the numerous agents which are not typically amenable to oral administration are biologically or chemically active peptides, such as calcitonin and insulin; polysaccharides, and in particular mucopolysaccharides including, but not limited to, heparin; heparinoids; 5 antibiotics; and other organic substances. These agents are rapidly rendered ineffective or are destroyed in the gastro-intestinal tract by acid hydrolysis, enzymes, or the like.

Earlier methods for orally administering vulnerable pharmacological agents have relied on the co-administration of adjuvants (e.g., resorcinols and 10 non-ionic surfactants such as polyoxyethylene oleyl ether and n-hexadecylpolyethylene ether) to increase artificially the permeability of the intestinal walls, as well as the co-administration of enzymatic inhibitors (e.g., pancreatic trypsin inhibitors, diisopropylfluorophosphate (DFF) and trasylol) to inhibit enzymatic degradation.

15 Liposomes have also been described as drug delivery systems for insulin and heparin. See, for example, U.S. Patent No. 4,239,754; Patel et al. (1976), *FEBS Letters*, Vol. 62, pg. 60; and Hashimoto et al. (1979), *Endocrinology Japan*, Vol. 26, pg. 337.

However, broad spectrum use of such drug delivery systems is 20 precluded because: (1) the systems require toxic amounts of adjuvants or inhibitors; (2) suitable low molecular weight cargos, i.e. active agents, are not available; (3) the systems exhibit poor stability and inadequate shelf life; (4) the systems are difficult to manufacture; (5) the systems fail to protect the active agent (cargo); (6) the systems adversely alter the active agent; or (7) the 25 systems fail to allow or promote absorption of the active agent.

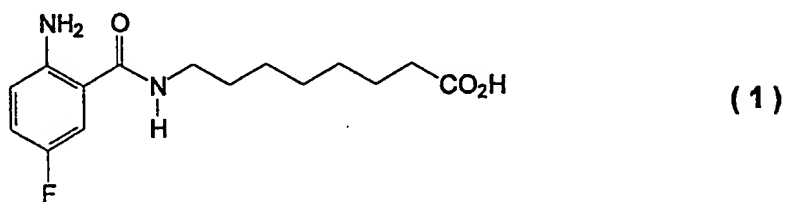
More recently, microspheres of artificial polymers of mixed amino acids (proteinoids) have been used to deliver pharmaceuticals. For example, U.S. Patent No. 4,925,673 describes drug-containing proteinoid microsphere carriers as well as methods for their preparation and use. These proteinoid 30 microspheres are useful for the delivery of a number of active agents.

There is still a need in the art for simple, inexpensive delivery systems which are easily prepared and which can deliver a broad range of active agents.

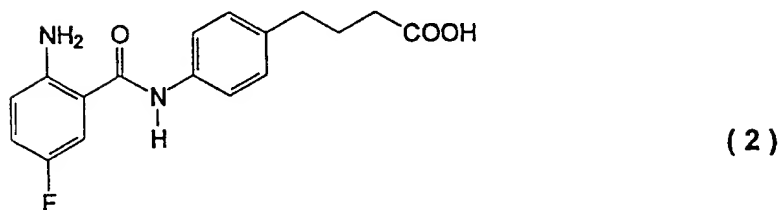
**SUMMARY OF THE INVENTION**

Compounds and compositions which are useful in the delivery of active agents are provided. These compositions include at least one active agent, preferably a biologically or chemically active agent, and at least one of

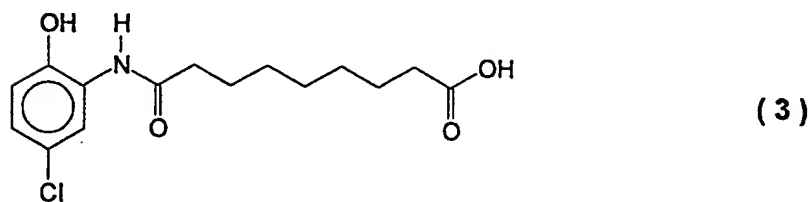
5 the following compounds 1-3, or salts thereof.



N-(2-amino-5-fluorobenzoyl)-8-aminocaprylic acid



4-(N-(5-fluoro-2-aminobenzoyl)-4-aminophenyl)butyric acid



8-(2-hydroxy-5-chloroanilino)octanoic acid

30 Compositions comprising the carrier compounds discussed above and active agents are effective in delivering active agents to selected biological systems.

**DETAILED DESCRIPTION OF THE INVENTION**

The specific compositions of the present invention include an active agent and a carrier. These compositions may be used to deliver various active agents through various biological, chemical, and physical barriers and are particularly suited for delivering active agents which are subject to environmental degradation. The compositions of the subject invention are particularly useful for delivering or administering biologically or chemically active agents to any animals such as birds including, but not limited to, chickens; mammals, such as primates and particularly humans; and insects.

Other advantages of the present invention include the use of easy to prepare, inexpensive raw materials. The compositions and the formulation methods of the present invention are cost effective, simple to perform, and amenable to industrial scale up for commercial production.

Subcutaneous, sublingual, and intranasal coadministration of an active agent, such as, for example, recombinant human growth hormone (rhGH); salmon calcitonin; heparin, including, but not limited to, low molecular weight heparin; parathyroid hormone; and compounds in compositions as described herein result in an increased bioavailability of the active agent compared to administration of the active agent alone.

**Active Agents**

Active agents suitable for use in the present invention include biologically or chemically active agents, chemically active agents, including, but not limited to, fragrances, as well as other active agents such as, for example, cosmetics.

Biologically or chemically active agents include, but are not limited to, pesticides, pharmacological agents, and therapeutic agents. For example, biologically or chemically active agents suitable for use in the present invention include, but are not limited to, peptides, and particularly small peptides; hormones, and particularly hormones which by themselves do not or only a fraction of the administered dose passes through the gastro-intestinal mucosa and/or are susceptible to chemical cleavage by acids and enzymes in the gastro-intestinal tract; polysaccharides, and particularly mixtures of muco-

polysaccharides; carbohydrates; lipids; or any combination thereof. Further examples include, but are not limited to, human growth hormones; bovine growth hormones; growth releasing hormones; interferons; interleukin-1; insulin; heparin, and particularly low molecular weight heparin; calcitonin; erythropoietin; 5 atrial naturetic factor; antigens; monoclonal antibodies; somatostatin; adrenocorticotropin, gonadotropin releasing hormone; oxytocin; vasopressin; cromolyn sodium (sodium or disodium chromoglycate); vancomycin; desferrioxamine (DFO); parathyroid hormone anti-microbials, including, but not limited to anti-fungal agents; or any combination thereof.

10

### Carriers

Although compounds 1-3 above have been found to act as carriers for the oral delivery of biologically or chemically active agents.

Properties of compounds 1-3 are listed in Table 1, below.

15

TABLE 1 - Carrier Properties

Compound	Anal. Calculated For					Found				Melting Point (°C)	Solubility
	C	H	N	S		C	H	N	S		
1	60.79	7.14	9.45			60.89	7.18	9.41		108-109	200 mg/mL slightly milky at pH 8.7
2	64.55	5.42	8.86			64.38	5.42	8.74		165-168	200 mg/mL milky suspension - pH = 8.44
3	57.42	6.42	4.46			57.30	6.38	4.39		119-120	200 mg/mL soluble - pH = 8.28



These carrier compounds or poly amino acids, and peptides, including the amino acids, may be used to deliver active agents including, but not limited to, biologically or chemically active agents such as for example, pharmacological and therapeutic agents.

- 5           An amino acid is any carboxylic acid having at least one free amine group and includes naturally occurring and synthetic amino acids.

Poly amino acids are either peptides or two or more amino acids linked by a bond formed by other groups which can be linked, e.g. an ester, anhydride, or an anhydride linkage.

- 10           Peptides are two or more amino acids joined by a peptide bond. Peptides can vary in length from dipeptides with two amino acids to poly peptides with several hundred amino acids. See Chambers Biological Dictionary, editor Peter M. B. Walker, Cambridge, England: Chambers Cambridge, 1989, page 215. Special mention is made of di-peptides, tri-peptides, tetra-peptides,  
15   and penta-peptides.

Salts such as, for example, sodium salt of these carrier compounds can be used as well.

These compounds are derived from amino acids.

- For example, these compounds may be prepared by reacting the  
20   single acid with the appropriate agent which reacts with free amino moiety present in the amino acids to form amides. Protecting groups may be used to avoid unwanted side reactions as would be known to those skilled in the art. See, U.S. patent application serial nos. 60/017,902, filed March 29, 1996; 08/414,654, filed March 31, 1995; 08/335,148, filed October 25, 1994; and  
25   60/003,111, filed September 1, 1995.

- The carrier compound may be purified by recrystallization or by fractionation on solid column supports. Suitable recrystallization solvent systems include acetonitrile, methanol and tetrahydrofuran. Fractionation may be performed on a suitable solid column supports such as alumina, using  
30   methanol/n-propanol mixtures as the mobile phase; reverse phase column supports using trifluoroacetic acid/acetonitrile mixtures as the mobile phase; and ion exchange chromatography using water as the mobile phase. When anion

exchange chromatography is performed, preferably a subsequent 0-500 mM sodium chloride gradient is employed.

### **Delivery Systems**

5           The compositions of the present invention may include one or more active agents.

          In one embodiment, compounds or salts of compounds 1-3 or poly amino acids or peptides that include at least one of these compounds or salts may be used directly as a delivery carrier by simply mixing one or more  
10   compound or salt, poly amino acid or peptide with the active agent prior to administration.

          The administration mixtures are prepared by mixing an aqueous solution of the carrier with an aqueous solution of the active ingredient, just prior to administration. Alternatively, the carrier and the biologically or  
15   chemically active ingredient can be admixed during the manufacturing process. The solutions may optionally contain additives such as phosphate buffer salts, citric acid, acetic acid, gelatin, and gum acacia.

          Stabilizing additives may be incorporated into the carrier solution. With some drugs, the presence of such additives promotes the stability and  
20   dispersibility of the agent in solution.

          The stabilizing additives may be employed at a concentration ranging between about 0.1 and 5 % (W/V), preferably about 0.5 % (W/V). Suitable, but non-limiting, examples of stabilizing additives include gum acacia, gelatin, methyl cellulose, polyethylene glycol, carboxylic acids and salts thereof,  
25   and polylysine. The preferred stabilizing additives are gum acacia, gelatin and methyl cellulose.

          The amount of active agent is an amount effective to accomplish the purpose of the particular active agent. The amount in the composition typically is a pharmacologically, biologically, therapeutically, or chemically  
30   effective amount. However, the amount can be less than a pharmacologically, biologically, therapeutically, or chemically effective amount when the composition is used in a dosage unit form, such as a capsule, a tablet or a liquid, because the dosage unit form may contain a multiplicity of carrier/biologically

or chemically active agent compositions or may contain a divided pharmacologically, biologically, therapeutically, or chemically effective amount. The total effective amounts can then be administered in cumulative units containing, in total, pharmacologically, biologically, therapeutically or chemically  
5 active amounts of biologically or pharmacologically active agent.

The total amount of active agent, and particularly biologically or chemically active agent, to be used can be determined by those skilled in the art. However, it has surprisingly been found that with some biologically or chemically active agents, the use of the presently disclosed carriers provides  
10 extremely efficient delivery, particularly in oral, intranasal, sublingual, intraduodenal, or subcutaneous systems. Therefore, lower amounts of biologically or chemically active agent than those used in prior dosage unit forms or delivery systems can be administered to the subject, while still achieving the same blood levels and therapeutic effects.

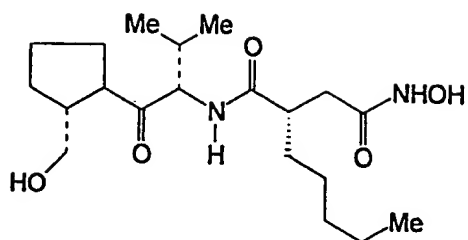
15 The amount of carrier in the present composition is a delivery effective amount and can be determined for any particular carrier or biologically or chemically active agent by methods known to those skilled in the art.

Dosage unit forms can also include any of excipients; diluents; disintegrants; lubricants; plasticizers; colorants; and dosing vehicles, including,  
20 but not limited to water, 1,2-propane diol, ethanol, olive oil, or any combination thereof.

Administration of the present compositions or dosage unit forms preferably is oral or by intraduodenal injection.

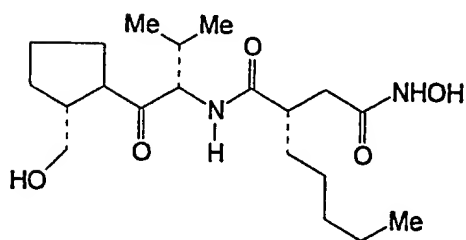
The delivery compositions of the present invention may also include  
25 one or more enzyme inhibitors. Such enzyme inhibitors include, but are not limited to, compounds such as actinonin or epiactinonin and derivatives thereof. These compounds have the formulas below:

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Actinonin

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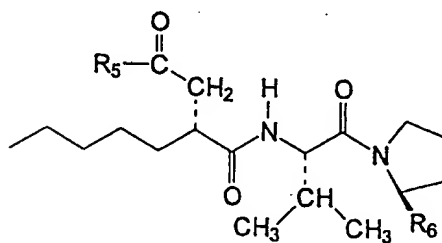


Epiactinonin

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- 20 Derivatives of these compounds are disclosed in U.S. Patent No. 5,206,384. Actinonin derivatives have the formula:

25



- 30 wherein  $R^5$  is sulfoxymethyl or carboxyl or a substituted carboxy group selected from carboxamide, hydroxyaminocarbonyl and alkoxycarbonyl groups; and  $R^6$  is hydroxyl, alkoxy, hydroxyamino or sulfoxyamino group. Other enzyme inhibitors include, but are not limited to, aprotinin (Trasylol) and Bowman-Birk inhibitor.

The compounds and compositions of the subject invention are useful for administering biologically or chemically active agents to any animals such as birds; mammals, such as primates and particularly humans; and insects. The system is particularly advantageous for delivering chemically or biologically  
5 or chemically active agents which would otherwise be destroyed or rendered less effective by conditions encountered before the active agent its target zone (i.e. the area in which the active agent of the delivery composition are to be released) and within the body of the animal to which they are administered. Particularly, the compounds and compositions of the present invention are useful  
10 in orally administering active agents, especially those which are not ordinarily orally deliverable.

### DESCRIPTION OF THE PREFERRED EMBODIMENTS

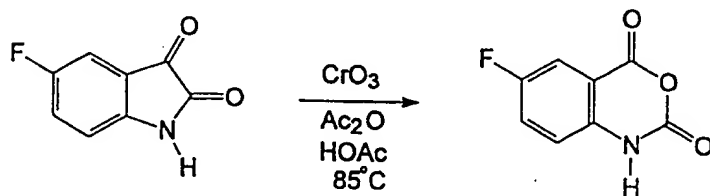
The following examples illustrate the invention without limitation.  
15 All parts are given by weight unless otherwise indicated.

#### Example 1 - Carrier Preparation

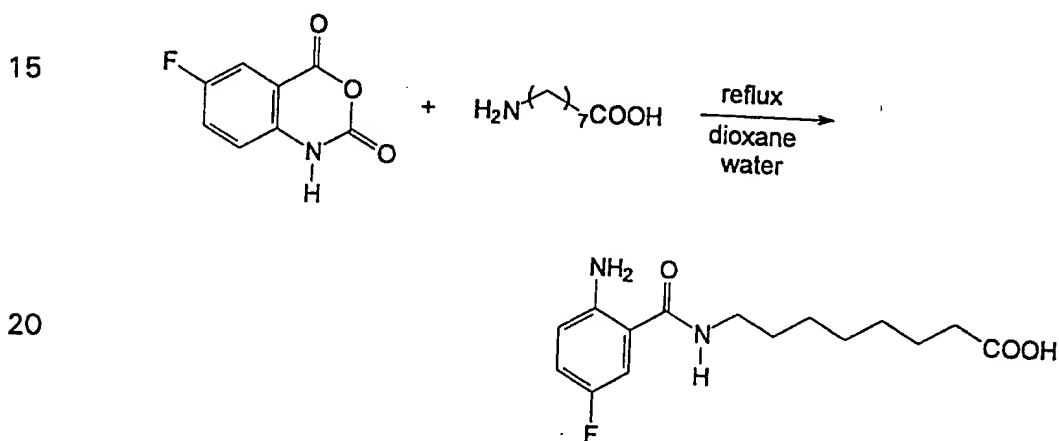
**General Preparations of Carriers.** The following procedures were used to prepare the compounds described herein.

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#### **Preparation of Compound 1.**



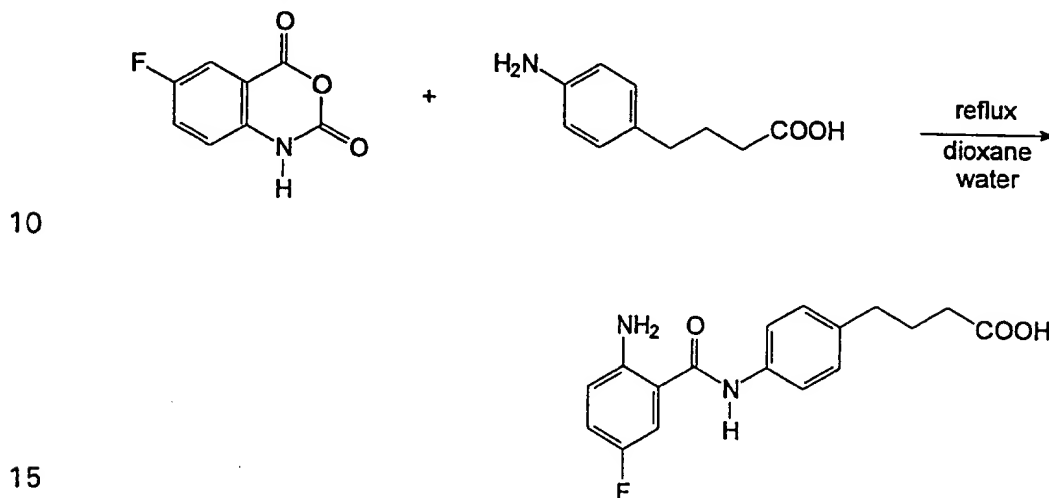
**Preparation of 5-Fluoroisatoic Anhydride.** Acetic anhydride (90.0 mL), 5-fluoroisatin (20.62 g, 0.125 mmol, 1.00 eq), and acetic acid (90 mL) were added to a 250 mL, three neck flask fitted with a magnetic stir bar and a condenser. The flask was placed in a water bath and heated to 85°C. Chromium (VI) oxide (20.36 g, 0.204 mol, 1.63 eq) was added in small portions (0.5 g size) over 40 min to the red solution. The reaction mixture was stirred for an additional 15 min and cooled to 10°C in an ice bath. The solid that formed was isolated by filtration. Washing with 400 mL of water removed most of the green color. The solid was taken up in 300 mL of 2:1 acetic acid/water, refiltered, and dried overnight in a 50°C vacuum oven. The 5-fluoroisatoic anhydride was isolated as a bright yellow solid (14.45 g, 64%).



**Preparation of N-(2-Amino-5-fluorobenzoyl)-8-aminocaprylic Acid (E-815).** A 50% (by weight) solution of potassium carbonate (11.2 mL, 16.8 mmol, 1.02 eq), 8-aminocaprylic acid (9.5 g, 59.7 mmol, 1.00 eq), 5-fluoroisatoic anhydride (10.82 g, 59.7 mmol, 1.00 eq), dioxane (40 mL), and water (5 mL) were added to a 100 mL round bottom flask equipped with a magnetic stir bar and a condenser. The red cloudy mixture was heated to 90°C for 2 hours (at which time the reaction was determined to have finished, by HPLC). The deep purple solution was cooled to 25°C and acidified to pH = 4.0 with 3% (by vol.) aqueous hydrochloric acid. The dark precipitate which formed was isolated by filtration. The solid was recrystallized from 50 mL of 65%

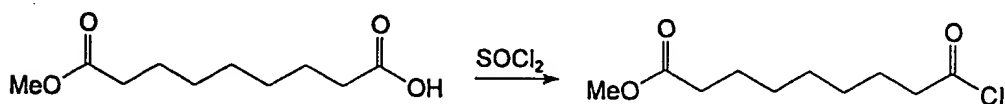
ethanol-water, recovered by filtration and dried over 6 hours in a 50°C vacuum oven. The N-(2-amino-5-fluorobenzoyl)-8-aminocaprylic acid was isolated as a light yellow solid (11.86 g, 67%), mp = 108-109°C.

5 **Preparation of Compound 2.**

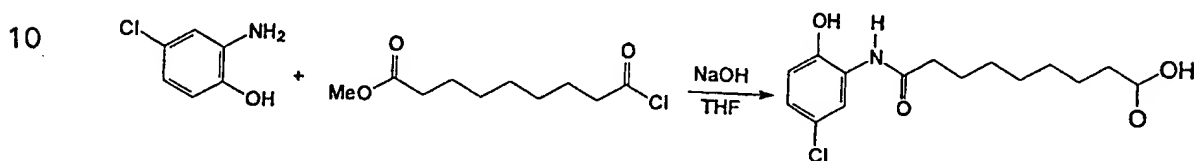


**Preparation of 4-(N-Amino-5-fluorobenzoyl)-4-aminophenyl)butyric Acid (E821).** 5-fluoroisatoic anhydride (7.10 g, 39.2 mmol, 1.00 eq), 4-(4-aminophenyl)butyric acid (7.02 g, 39.2 mmol, 1.00 eq), dioxane (80 mL), and water 20 mL) were added to a 100 mL round bottom flask equipped with a magnetic stir bar and a condenser. The red cloudy mixture was heated to 90°C for 6 hours (at which time the reaction was determined to have finished, by HPLC). The reaction mixture was cooled to 30°C and filtered to remove a small amount of solid. The filtrate was concentrated to an orange brown solid. The solid was recrystallized from 50 mL of ethanol (1st crop) and 80% ethanol-water (2nd crop), recovered by filtration and dried over 6 hours in a 50°C vacuum oven. The 4-(N-(2-amino-5-fluorobenzoyl)-4-aminophenyl)butyric was isolated as a light tan solid (7.11 g, 57%), mp = 169-170°C.

30 **Preparation of Compound 3.**



**Methyl Azeloyl Chloride.** A mixture of methyl hydrogen azelate (14.68 g, 72.58 mmol) and thionyl chloride (5.6 mL, 76.75 mmol) was refluxed for 3 h. The excess thionyl chloride was removed *in vacuo*. The residue was  
5 distilled under reduced pressure. The fractions between 130-134°C at 3.5 mm/Hg were combined affording methyl azeloyl chloride as a colorless oil (14 g, 87%).



15 **Preparation of 8-(2-hydroxy-5-chloroanilino)octanoic acid.**

To a cold solution of 2-amino-4-chlorophenol (2.56 g, 17.83 mmol) in tetrahydrofuran (40 mL) was added a solution of hydroxide (0.72 g, 18 mmol) in water (15 mL). The mixture was stirred at 0°C for 5 min. A solution of methyl azeloyl chloride (3.9 g, 17.67 mmol) in tetrahydrofuran (10 mL) was  
20 added dropwise to this mixture. The resulting mixture was stirred at 0°C, then gradually warmed to room temperature, and stirred at room temperature overnight. A solution of sodium hydroxide (2 N, 25 mL) was added to the reaction mixture. The mixture was stirred at room temperature and monitored by TLC. When the starting material was no longer visible, the reaction mixture  
25 was concentrated *in vacuo*. The residue was acidified to pH 2 and the precipitated solid was collected by filtration. This crude product was dissolved in methanol (50 mL), decolorized with activated charcoal, and filtered. A small amount of acetone and water was added to the filtrate and the mixture refrigerated overnight. A solid was formed, collected by filtration, washed with  
30 water, and dried to give E-804 as a pale yellow, crystalline solid (3.0 g, 54%); mp 117-118°C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 7.96 (d, *J* = 2.5 Hz, 1H), 6.95 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.85 Hz, 1H), 2.39 (t, *J* = 7.3 Hz, 2H), 2.19 (t, *J* = 7.3 Hz,



2H), 1.40-1.61 (m, 4H), 1.20-1.35 (m, 6H). Anal. Calcd for  $C_{15}H_{20}ClNO_4 \cdot C$ , 57.42; H, 6.42; N, 4.46. Found: C, 57.24; H, 6.30; N, 4.41.

**Example 2 - Parathyroid Hormone Dosing Solutions**

- 5                      Oral gavage ("PO") dosing solution containing 300 mg/kg of carrier compound 1, 2 or 3 and 100  $\mu$ g/kg of parathyroid hormone in water were prepared. The dosing solution is designated P- carrier number - DS.

**Example 3 - *In vivo* Parathyroid Hormone Delivery**

- 10                      Male Sprague-Dawley rats weighing between 200-250g were fasted for 24 hours and were administered ketamine (44 mg/kg) and chlorpromazine (1.5 mg/kg) 15 minutes prior to dosing. The rats were administered one of dosing solutions P-1-DS, P-2-DS, or P-3-DS by oral gavage ("PO") or intra-colonic instillation ("IC"). Blood samples were collected serially
- 15 from the tail artery for serum determination of parathyroid hormone concentration. Serum parathyroid hormone concentrations were quantified by a parathyroid hormone immunoaccuracy test host.

Results are illustrated in Table 2, below.

TABLE 2 - <i>In vivo</i> Parathyroid Hormone Delivery	
Dosing Solution	Cmax (ng/ml)
P-1-DS	11.93
P-1-DS	19.75
P-1-DS	38.37
Average P-1-DS	23.35
P-2-DS	36.05
P-2-DS	222.16
P-2-DS	51
Average P-2-DS	103.1
P-3-DS	53.03
P-3-DS	616.61
P-3-DS	44.33
Average P-3-DS	237.99

**Examples 4 - Recombinant Human Growth Hormone Dosing Solutions**

Oral gavage dosing solutions containing 300 mg/kg of carrier compound and 6 mg/kg of rHGH or 25 mg/kg of carrier 3 and 1 mg/kg of rHGH, both in phosphate buffer were prepared.

The dosing solutions are designated R- carrier number - DS.

**Example 5 - *In Vivo* Recombinant Human Growth Hormone Delivery**

Male Sprague-Dawley rats weighing 200-250g were fasted for 24 hours and administered ketamine (44 mg/kg) and chlorpromazine (1.5 mg/kg) 15 minutes prior to dosing. The rats were administered one of the dosing solutions of Example 3 by oral gavage. Blood samples were collected serially from the tail artery for determination of serum rHGH concentrations. Serum rHGH concentrations were quantified by an rHGH immunoassay test kit.

Results are illustrated in Table 3, below.

TABLE 3 - <i>In Vivo</i> Recombinant Human Gr wth Hormone Delivery	
Dosing Solution	Cmax (ng/ml)
R-2-DS	115.7
R-3-DS	86.37
R-3-DS	123.34
Average R-3-DS	104.9

10                   The above mentioned patents, applications, test methods, and publications are hereby incorporated by reference in their entirety.

                  Many variations of the present invention will suggest themselves to those skilled in the art in light of the above detailed description. All such obvious variations are within the full intended scope of the appended claims.

**WHAT IS CLAIMED IS:**

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2 1. A composition comprising:

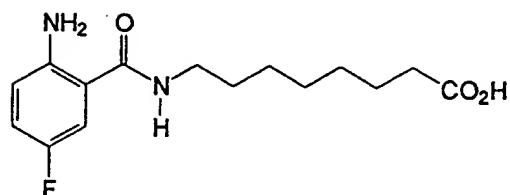
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(A) at least one active agent; and

4

(B) at least one carrier selected from the group consisting of

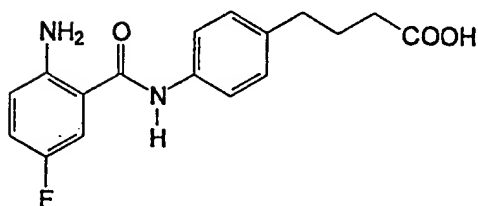
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( 1 )

N-2(amino-5-fluorobenzoyl)-8-aminocaprylic acid

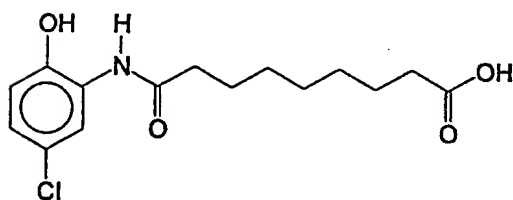
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( 2 )

4-(N-(5-fluoro-2-aminobenzoyl)-4-aminophenyl)butyric acid

7



( 3 )

8-(2-hydroxy-5-chloroanilino)octanoic acid

5 and a salt of any of the foregoing.

1                   2.     A composition as defined in claim 1, wherein said active  
2 agent is selected from the group consisting of a biologically active agent, a  
3 chemically active agent, or a combination thereof.

1                   3.     A composition as defined in claim 2, wherein said biologically  
2 active agent comprises at least one peptide, mucopolysaccharide, carbohydrate,  
3 or lipid.

1                   4.     A composition as defined in claim 2, wherein said biologically  
2 active agent is selected from the group consisting of human growth hormone,  
3 bovine growth hormone, growth hormone-releasing hormone, an interferon,  
4 interleukin-II, insulin, heparin, low molecular weight heparin, calcitonin,  
5 erythropoietin, atrial natriuretic factor, an antigen, a monoclonal antibody,  
6 somatostatin, adrenocorticotropin, gonadotropin releasing hormone, oxytocin,  
7 vasopressin, cromolyn sodium, vancomycin, parathyroid hormone,  
8 desferrioxamine (DFO), or any combination thereof.

1                   5.     A composition as defined in claim 4, wherein said biologically  
2 active agent comprises an interferon, interleukin-II, insulin, heparin, low  
3 molecular weight heparin, calcitonin, oxytocin, vasopressin, vancomycin, DFO,  
4 parathyroid hormone, and combinations thereof.

1                   6.     A composition as defined in claim 1, wherein said carrier  
2 comprises a poly(amino acid).

1                   7.     A composition as defined in claim 1, wherein said carrier  
2 comprises a polypeptide.

1                   8.     A dosage unit form comprising  
2                   (A)    a composition as defined in claim 1; and  
3                   (B)    (a)    an excipient

- 4 (b) a diluent,
- 5 (c) a disintegrant,
- 6 (d) a lubricant,
- 7 (e) a plasticizer,
- 8 (f) a colorant,
- 9 (g) a dosing vehicle, or
- 10 (h) any combination thereof.

1 9. A composition as defined in claim 8, wherein said active  
2 agent is selected from the group consisting of a biologically active agent, a  
3 chemically active agent, or a combination thereof.

1 10. A composition as defined in claim 9, wherein said biologically  
2 active agent comprises at least one peptide, mucopolysaccharide, carbohydrate,  
3 or lipid.

1 11. A composition as defined in claim 9, wherein said biologically  
2 active agent is selected from the group consisting of human growth hormone,  
3 bovine growth hormone, growth hormone-releasing hormone, an interferon,  
4 interleukin-II, insulin, heparin, low molecular weight heparin, calcitonin,  
5 erythropoietin, atrial natriuretic factor, an antigen, a monoclonal antibody,  
6 somatostatin, adrenocorticotropin, gonadotropin releasing hormone, oxytocin,  
7 vasopressin, cromolyn sodium, vancomycin, parathyroid hormone,  
8 desferrioxamine (DFO), or any combination thereof.

1 12. A composition as defined in claim 11, wherein said  
2 biologically active agent comprises an interferon, interleukin-II, insulin, heparin,  
3 low molecular weight heparin, calcitonin, oxytocin, vasopressin, vancomycin,  
4 DFO, parathyroid hormone, and combinations thereof.

1 13. A dosage unit form comprising  
2 (A) a composition as defined in claim 6; and  
3 (B) (a) an excipient

- 4 (b) a diluent,
- 5 (c) a disintegrant,
- 6 (d) a lubricant,
- 7 (e) a plasticizer,
- 8 (f) a colorant,
- 9 (g) a dosing vehicle, or
- 10 (h) any combination thereof.

1 14. A composition as defined in claim 13, wherein said active  
2 agent is selected from the group consisting of a biologically active agent, a  
3 chemically active agent, or a combination thereof.

1 15. A composition as defined in claim 14, wherein said  
2 biologically active agent comprises at least one peptide, mucopolysaccharide,  
3 carbohydrate, or lipid.

1 16. A composition as defined in claim 14, wherein said  
2 biologically active agent is selected from the group consisting of human growth  
3 hormone, bovine growth hormone, growth hormone-releasing hormone, an  
4 interferon, interleukin-II, insulin, heparin, low molecular weight heparin,  
5 calcitonin, erythropoietin, atrial natriuretic factor, an antigen, a monoclonal  
6 antibody, somatostatin, adrenocorticotropin, gonadotropin releasing hormone,  
7 oxytocin, vasopressin, cromolyn sodium, vancomycin, parathyroid hormone,  
8 desferrioxamine (DFO), or any combination thereof.

1 17. A composition as defined in claim 16, wherein said  
2 biologically active agent comprises an interferon, interleukin-II, insulin, heparin,  
3 low molecular weight heparin, calcitonin, oxytocin, vasopressin, vancomycin,  
4 DFO, parathyroid hormone, and combinations thereof.

1 18. A dosage unit form comprising  
2 (A) a composition as defined in claim 7; and  
3 (B) (a) an excipient

- 4 (b) a diluent,
- 5 (c) a disintegrant,
- 6 (d) a lubricant,
- 7 (e) a plasticizer,
- 8 (f) a colorant,
- 9 (g) a dosing vehicle, or
- 10 (h) any combination thereof.

1 19. A composition as defined in claim 18, wherein said active  
2 agent is selected from the group consisting of a biologically active agent, a  
3 chemically active agent, or a combination thereof.

1 20. A composition as defined in claim 19, wherein said  
2 biologically active agent comprises at least one peptide, mucopolysaccharide,  
3 carbohydrate, or lipid.

1 21. A composition as defined in claim 19, wherein said  
2 biologically active agent is selected from the group consisting of human growth  
3 hormone, bovine growth hormone, growth hormone-releasing hormone, an  
4 interferon, interleukin-II, insulin, heparin, low molecular weight heparin,  
5 calcitonin, erythropoietin, atrial natriuretic factor, an antigen, a monoclonal  
6 antibody, somatostatin, adrenocorticotropin, gonadotropin releasing hormone,  
7 oxytocin, vasopressin, cromolyn sodium, vancomycin, parathyroid hormone,  
8 desferrioxamine (DFO), or any combination thereof.

1 22. A composition as defined in claim 21, wherein said  
2 biologically active agent comprises an interferon, interleukin-II, insulin, heparin,  
3 low molecular weight heparin, calcitonin, oxytocin, vasopressin, vancomycin,  
4 DFO, parathyroid hormone, and combinations thereof.

1 23. A dosage unit form as defined in claim 8, comprising a tablet,  
2 a capsule, or a liquid.



1                    24. A dosage unit form as defined in claim 23, wherein said  
2 dosing vehicle is selected from the group consisting of water, 1,2-propane diol,  
3 ethanol, or any combination thereof.

1                    25. A dosage unit form as defined in claim 13, comprising a  
2 tablet, a capsule, or a liquid.

1                    26. A dosage unit form as defined in claim 25, wherein said  
2 dosing vehicle is selected from the group consisting of water, 1,2-propane diol,  
3 ethanol, or any combination thereof.

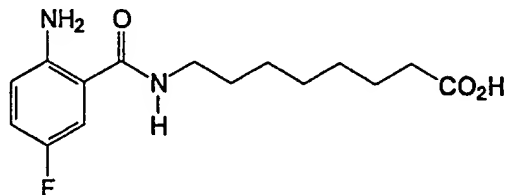
1                    27. A dosage unit form as defined in claim 18, comprising a  
2 tablet, a capsule, or a liquid.

1                    28. A dosage unit form as defined in claim 27, wherein said  
2 dosing vehicle is selected from the group consisting of water, 1,2-propane diol,  
3 ethanol, or any combination thereof.

1                    29. A method for administering a biologically-active agent to an  
2 animal in need of said agent, said method comprising administering orally to said  
3 animal a composition as defined in claim 2.

4                    30. A compound selected from the group consisting of

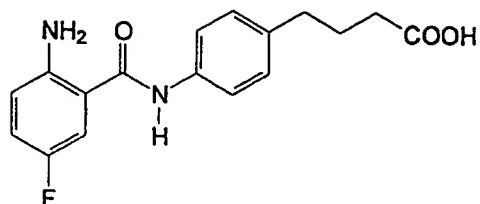
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(1)

N-2(amino-5-fluorobenzoyl)-8-aminocaprylic acid

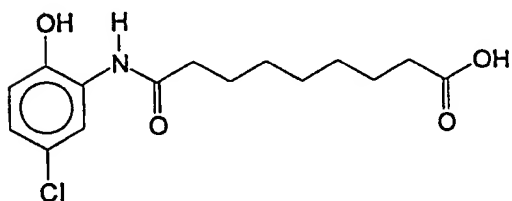
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( 2 )

4-(N-(5-fluoro-2-aminobenzoyl)-4-aminophenyl)butyric acid

7



( 3 )

8-(2-hydroxy-5-chloroanilino)octanoic acid

5 and a salt of any of the foregoing.

1 31. A method for preparing a composition, said method  
2 comprising mixing:

- 3 (A) at least one active agent;  
4 (B) at least one compound as defined in claim 31; and  
5 (C) optionally, a dosing vehicle.

## INTERNATIONAL SEARCH REPORT

International application No. .  
PCT/US98/07045

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC(6) : C07C 231/00; C07C 229/00 US CL : 554/62; 562/449, 456 According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) U.S. : 554/62; 562/449, 456  Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CAPLUS ON STN		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y,P	US 5,643,957 A (LEONE-BAY et al.) 01 July 1997, see entire document.	1-31
Y,P	US 5,650,386 A (LEONE-BAY et al.) 22 July 1997, see entire document.	1-31
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* "A" "B" "L" "O" "P"	Special categories of cited documents: document defining the general state of the art which is not considered to be of particular relevance earlier document published on or after the international filing date document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) document referring to an oral disclosure, use, exhibition or other means document published prior to the international filing date but later than the priority date claimed	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art *A* document member of the same patent family
Date of the actual completion of the international search 09 JUNE 1998		Date of mailing of the international search report 16.07.1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230		Authorized officer <i>Brian J. Davis</i> BRIAN J. DAVIS Telephone No. (703) 308-1235